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(Article begins on next page)

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Anakinra for corticosteroid-dependent and colchicine-resistant recurrent pericarditis: the IRAP registry (International Registry of Anakinra for Pericarditis)

Massimo Imazio[1*], MD, FESC; Alessandro Andreis[1*], MD; Gaetano Maria De Ferrari[1], MD, Paul Cremer[2], MD, Vartan Mardigyan[3], MD, FRCPC, S. Allen Luis[5], MD, Giuseppe Lopalco[6], MD Giacomo Emmi[7], MD; Dor Lotan[8], MD, Federica Bello[7], MD; Laeora Berkson[3], MD, FRCPC, MHPE, Alida Linda Caforio[9], MD; George Lazaros[10], MD, FESC; Marzia De Biasio[11], MD, Luca Cantarini[12], MD; Lorenzo Dagna[13], MD, Andrea Cerne Cercek[14], MD, Giacomo De Luca[11], MD; Carla Giustetto[1], MD, Florenzo Iannone, MD,[6] Silvia Maestroni[4], MD; Renzo Marcolongo[9], MD, Emanuele Pivetta, MD[15]; Mauro Rinaldi[1], MD, Enrico Tombetti, MD,[4] Dimitrios Tousoulis[10], MD, FESC, Dimitrios Vassilopoulos[10], MD; Yehuda Adler, MD[6**] Jae K. Oh[5**], MD, Allan L. Klein[2**], MD, Antonio Brucato[4**], MD

*These authors equally contributed to this paper as first co-authors.

**These authors equally contributed to this paper as last Senior co-authors.

[1] *Coordinating Center: University Cardiology, A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy*

[2] *Heart & Vascular Institute, Cleveland Clinic, Cleveland, Ohio, United States*

[3] *McGill University, Jewish General Hospital, Montreal, Canada*

[4] *Internal Medicine Division, Ospedale Papa Giovanni XXIII, Bergamo, Italy and University of Milan, Milano, Italy*

[5] *Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, United States*

[6] *Rheumatology Unit; Department of Emergency and Organ Transplantation (DETO); Polyclinic Hospital, University of Bari, Bari, Italy*

[7] *Careggi Hospital, Florence, Italy*

[8] *Chaim Medical Center, Tel Hashomer, Israel*

[9] *University Cardiology, Policlinico Padova, Padua, Italy*

[10] *University Cardiology, Hyppokration Hospital and University of Athens, Athens, Greece*

[11] *Cardiology Department, Udine Hospital, Udine, Italy*

[12] *Research Center of Systemic Autoinflammatory Diseases, Behcet's Disease and Rheumatology-Ophthalmology Collaborative Uveitis Center, Rheumatology Unit, Policlinico Le Scotte, University of Siena, Siena, Italy*

[13] *Immunology, Rheumatology, Allergology and Rare diseases Department, San Raffaele Hospital, Milan, Italy*

[14] *Department of Cardiology, University Medical Center Ljubljana, Slovenia*

[15] *Epidemiology Department, Università degli Studi di Torino, Turin, Italy*

Conflicts of interest: MI and AB have participated as advisory board members for SOBI (Swedish Orphan Biovitrum AB, Stockholm, Sweden).

The present study complied with the Declaration of Helsinki and subsequent modifications. The study was approved by the ethics committees at each participating center. All patients provided written informed consent.

Corresponding author

Massimo Imazio, MD, FESC

University Cardiology, AOU Città della Salute e della Scienza di Torino

Corso Bramante 88, 10126 Turin, Italy; Business phone:+39 0116335570,

E-mail: massimo_imazio@yahoo.it; massimo.imazio@unito.it

ABSTRACT (256 words)

Aims. Corticosteroid-dependent,colchicine-resistant refractory recurrent pericarditis (RRP) is challenging since resistant to conventional treatment (NSAIDs, colchicine, and corticosteroids). Interleukin-1 blockade with anakinra may be beneficial in RRP according to case reports, small case series and a single RCT on 21 patients. This registry was aimed to evaluate anakinra efficacy and safety in a “real world” population.

Methods and Results. This international multicenter registry enrolled 224 consecutive RRP patients (aged 46±14 years old, 63% females, 5.3±3.7 recurrences, 75% idiopathic etiology) with a mean disease duration of 27 months. Patients had C-reactive protein elevation in 91%, pericardial effusion in 88% of cases, and were treated with anakinra 100mg/day sc for a median time of 6 months (IQR,3-12). Pericarditis recurrence rate was the primary endpoint. ED admissions, hospitalizations and adverse events (AE) were secondary endpoints. Anakinra reduced pericarditis recurrences (6-fold reduction, from 2.33 to 0.39 flares-patient/year), ED admissions (11-fold reduction, from 1.08 to 0.10 admissions-patient/year), hospitalizations (7-fold reduction, from 0.99 to 0.13 hospitalizations-patient/year) and corticosteroids use (from 80% before anakinra to 27% after treatment).

AE occurred in 44% patients, without severe AE, mostly transitory skin reaction at the injection site. Seven patients (3%) needed anakinra withdrawal because of AE. A full-dose treatment duration of at least 3 months followed by a tapering period of at least 3 months were the therapeutic schemes associated with a lower risk of recurrence.

Conclusion. Anakinra is efficacious and safe in the long-term reduction of recurrences in RRP patients, furthermore decreasing ED admissions/hospitalizations and corticosteroids-dependence. Anakinra efficacy may be further increased by proper treatment protocols.

KEYWORDS:

Anakinra; recurrent pericarditis; interleukin-1 inhibition; interleukin-1β receptor antagonist; colchicine;

INTRODUCTION

Acute pericarditis is the most common form of pericardial disease, accounting for approximately 5% emergency department admissions for non-ischemic chest pain. Recurrent pericarditis affects up to 30% patients after a first episode, raising up to 50% in those who are not treated with colchicine and with multiple recurrences[1,2]. Possible treatments for the management of recurrences include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, immunomodulatory agents and pericardiectomy[3]. Patients with inadequate clinical response to conventional medical therapy (NSAIDs, colchicine, corticosteroids) and multiple unsuccessful attempts of corticosteroids tapering may develop tenacious forms of corticosteroid-dependent and colchicine-resistant refractory recurrent pericarditis (RRP), resulting in severe impairment of their quality of life. These patients have a challenging clinical management because of refractory symptoms and high prevalence of side effects due to chronic treatment with corticosteroids[4].

Although the pathogenesis of idiopathic recurrent pericarditis has not been fully explained lacking suitable animal models, according to recent theories[5,6] an amplified and self-sustained auto-inflammatory or auto-immune response following exogenous or endogenous triggers may explain incessant and recurrent pericarditis. Interleukin-1 blockade with anakinra is of growing interest in this setting because it may have the potential to dramatically reduce pericarditis recurrences, although strong evidence-based data are lacking in literature[7]. Indeed, current knowledge about anakinra use in RRP patients is based on 14 case reports[8–21], 4 case series on 10-14 patients[22–25], one randomized and controlled trial on 21 patients[26]. The generalizability of such limited findings in a real-world clinical setting, involving different patient populations and single center practice is a key question. The IRAP international, all-comers, multicenter registry was designed to specifically investigate this question.

The aim of this registry was to verify and evaluate the long-term efficacy and safety of anakinra in the treatment of corticosteroid-dependent and colchicine-resistant recurrent pericarditis in “real world” population.

METHODS

Study Design

The International Registry of Anakinra for Pericarditis (IRAP) is an international, all-comers, multicenter observational cohort study involving 14 referral centers for pericardial diseases across 6 different countries (see appendix A). The present study complied with the Declaration of Helsinki and subsequent modifications. The study was approved by the Ethical Committees at each participating center. All patients provided written informed consent. All consecutive patients afferent for RRP at each clinical site between 2014 and 2018 were enrolled at the time of a pericarditis recurrence if they were eligible to receive anakinra treatment according to local and international guidelines and were adult (>18 years old).

Inclusion and exclusion criteria

All patients eligible for inclusion in the present registry had corticosteroid-dependent and colchicine-resistant refractory recurrent pericarditis (RRP), defined as a first episode of acute pericarditis followed by a minimum of 2 recurrences despite guideline-based traditional medical treatment (NSAIDs, colchicine, corticosteroids). Corticosteroid-dependence was defined as the impossibility to withdraw steroids without incurring in a pericarditis recurrence. The first episode of pericarditis was diagnosed in the presence of at least 2 of the following criteria: pericarditic chest pain (sharp, pleuritic, improved by sitting up and leaning forward), friction rubs, ST-segment elevation or PR-segment depression on electrocardiogram, new or worsening pericardial effusion. A recurrence was

diagnosed when pericarditic chest pain reoccurred along with 1 or more of the following signs: fever, friction rubs, electrocardiographic changes, new or worsening pericardial effusion, CRP elevation.[1,2,27].

Exclusion criteria were specific contraindications to anakinra treatment: hypersensitivity to the active substance or to E. coli-derived proteins, neutropenia (absolute neutrophil count <1,5x10^9/L); active tubercular infection; active cancer.

Study Protocol

Enrolled patients received anakinra 100 mg once daily by subcutaneous (sc) injection. Concomitant medical treatment for pericarditis (NSAIDs, colchicine, corticosteroids) was maintained or tapered and suspended according to clinician choice based on patient evaluation. Clinical, laboratory testing, electrocardiographic and echocardiographic assessment were performed in all patients at the time of enrollment, according to local practice and following international guidelines.

Study End-points

The primary end-point was the variation of pericarditis recurrence rate after the initiation of anakinra treatment. The secondary end-points were: the variation of emergency department (ED) access rate and hospitalization rate after the after the initiation of anakinra treatment; the prevalence of patients on corticosteroid treatment after the initiation of anakinra treatment.

The occurrence of any adverse event (AE) and AE-related drug discontinuation was recorded and assessed as a safety end-point.

Statistical analysis

Blinded and independent analysis of data was performed by AA, GMDF, and EP in Turin (Coordinating Center). This cohort study followed the recommendations of the STROBE statement[28]. A minimum sample size of 24 patients was estimated to be sufficient to detect a difference in recurrence rate from 80% before Anakinra to 10% after Anakinra, based on previous evidences in literature[8–21,26], with a power of 90% at a confidence level of 95%. Continuous variables, presented as means and standard deviations, were compared by non-parametric tests: Mann-Whitney's test was used for independent data and Wilcoxon's signed-rank test for paired data (pre-post evaluations). Categorical variables, presented as counts and percentages, were compared using the chi-square test with Yates' correction or Fisher's exact test as appropriate. The survival probability and the freedom from adverse events were evaluated with the Kaplan-Meier curves, compared by the Mantel-Cox test. All analyses were performed using the SPSS version 18.0 (SPSS, Inc., Chicago, Illinois) and a two-sided significance level of <0.05 was considered statistically significant.

RESULTS

Population characteristics

A total of 224 RRP patients were included in the present registry, in a total of 14 centers across 6 different countries. The inclusion rate ranged from 1 to 53 patients, based on center volume and local practice (see appendix A). Each center enrolled consecutive patients in order to reproduce real-life practice and avoid any selection bias. Baseline population characteristics are reported in Table 1.

Table 1 – Participants characteristics at enrollment

Characteristics at enrollment	Population (n=224)
Age, years	46±14
Female gender	140 (63%)
Pericardial disease duration, months	27±32
Previous pericarditis recurrences	5.3±3.7
range	(2 - 27)
Previous ED admissions	2.5±2.8
range	(0 - 15)
Previous hospitalizations	2.2±2.1
range	(0 - 12)
Etiology	
Idiopathic	167 (75%)
Post-cardiac injury syndrome	28 (13%)
Autoimmune disease	21 (9%)
Autoinflammatory disease	5 (2%)
Attinic	2 (0.7%)
Traumatic	1 (0.3%)
CRP elevation	203 (91%)
Pericardial effusion	196 (88%)
Mild	101 (45%)
Moderate	48 (21%)
Severe	23 (10%)
Tamponade	24 (11%)
Therapy	
NSAIDs	170 (76%)
Colchicine	198 (88%)
Corticosteroids	180 (80%)
Triple therapy (NSAIDs + colchicine + corticosteroids)	141 (63%)

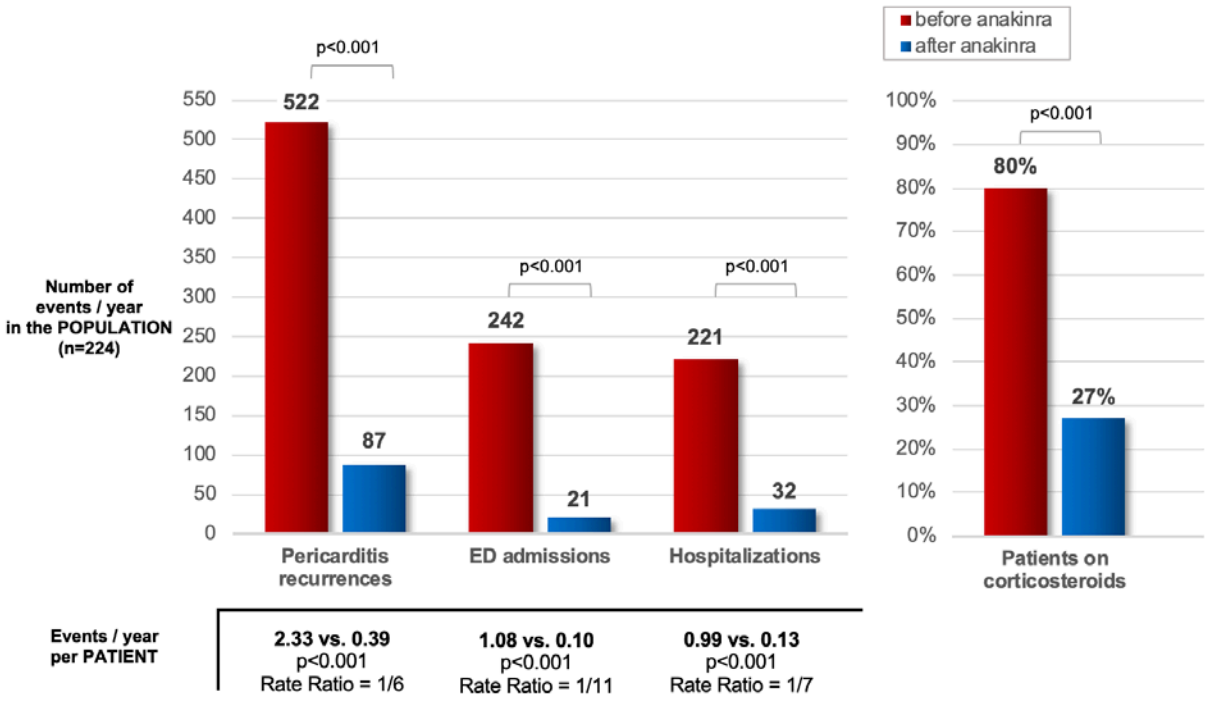
Values are presented as No. (%) or mean±standard deviation), range (minimum - maximum)
ED = emergency department
NSAIDs = non-steroidal anti-inflammatory drugs
CRP = C-reactive protein

Patients included in the registry had a mean age of 46 years old (range, 18-84), 140 (63%) were of female gender. Pericardial disease duration before the enrollment was 27±32 months, with 5.3±3.7 previous recurrences (range, 2-27), 2.5±2.8 ED admissions (range, 0-15) and 2.2±2.1 hospitalizations (range, 0-12). Recurrence rate before starting anakinra was 2.33 flares-patient/year, implying a mean of 1 recurrence every 157 days. ED admission rate was 1.08 admissions-patient/year while hospitalization rate was 0.99 hospitalizations-patient/year before starting anakinra.

All patients were diagnosed with recurrent pericarditis at the time of enrollment. Most patients had an idiopathic etiology (167 patients, 75%), CRP elevation (203 patients, 91%) and echocardiographic evidence of pericardial effusion (196 patients, 88%). At the time of

enrollment, medical treatment included NSAIDs in 170 patients (76%), colchicine in 198 patients (88%), and corticosteroids in 180 patients (80%).

FIGURE 1



Pericarditis recurrences after anakinra

During a follow-up of 3889 months-patient, one or more pericarditis recurrences were observed in 78 patients, with a flare-free time of 12±11 months (range, 0.33-48). Multiple recurrences were observed in 27 patients.

After anakinra initiation, a mean of 0.6±1 recurrences (range, 0-7) were observed. Recurrence rate after starting anakinra was 0.39 flares-patient/year, implying a mean of 1 recurrence every 939 days. Overall, an 83% reduction in recurrence rate was observed ($p<0.001$, rate ratio 0.17, 95% CI 0.14 - 0.20), equivalent to 1.94 less flares-patient/year.

At 36 months after anakinra initiation, 72% patients experienced none or at most one recurrence: respectively 43% patients were in stable remission without any recurrence while 29% patients had a single recurrence over a period of 36 months. The remaining 29% patients had two or more recurrences during the follow-up (range, 2-7).

ED admissions and hospitalizations after anakinra

During the follow-up a mean of 0.1±0.5 ED admissions (range, 0-4) and 0.2±0.5 hospitalizations (range, 0-2) were observed, corresponding to respectively 0.10 ED admissions-patient/year and 0.14 hospitalizations-patient/year. Compared to the period prior to treatment initiation, it was observed a reduction of 91% for ED admissions ($p<0.001$, rate ratio 0.09, 95% CI 0.06 - 0.13) and 86% for hospitalizations ($p<0.001$, rate ratio 0.14, 95% CI 0.11 - 0.19).

Twenty patients (8.9%) were admitted to cardiac surgery department and underwent pericardiectomy after 10±9 months (range, 1.8-38). These patients discontinued treatment with anakinra and terminated the follow-up observation by the time of intervention.

Corticosteroid-dependence after anakinra

Although all enrolled patients were corticosteroid-dependent, at the exact time of enrollment 180 patients (80%) were still on active treatment with steroids. After the initiation of anakinra treatment, during the follow up only 61 patients (27%) remained on active treatment. In all other patients, steroids could be tapered and discontinued without any symptom recurrence.

After starting anakinra, colchicine was continued in most patients. During the follow-up, 131 patients (58%) were still on active treatment. NSAIDs were withdrawn in most patients and only 54 (24%) were still on active treatment during the follow-up.

Adverse events

Adverse events were observed in 99 patients (44%), as described in Table 2.

Most frequent AE was a transient skin reaction at injection site (associated with erythema, itchy wheals, ecchymosis, pain), which occurred in 86 patients (38%), 13±16 days after the beginning of treatment. Three patients (1.3%) required permanent drug discontinuation because of intolerable symptoms.

Arthralgias and myalgias were reported by 13 patients (6%) during the treatment. One of these patients (0.4%) needed drug withdrawal.

Seven patients (3%) had a mild transient transaminases elevation (SGOT, SGPT) without any signs or symptoms of hepatic failure.

Infections were observed in 6 patients (3%) during the follow-up: two respiratory infections (bronchopneumonia), four skin and soft-tissue infections (skin abscess, cryptococcus neoformans necrotizing cellulitis, lymphocele infection, pelvic cyst infection). In half cases anakinra was temporarily suspended and only one patient was permanently discontinued (patient with skin abscess). In all patients infections were successfully resolved with proper treatment.

A transient neutropenia was observed in 3 patients (1%), not associated with clinical events, with subsequent resolution.

Some other AE, with questionable association with anakinra treatment, were reported by single patients as follows: hypereosinophilia, mild serotine fever, hot flashes and sweating, perforated diverticulitis, optic neuritis.

Overall, 7 patients (3%) discontinued permanently anakinra after an AE, as aforementioned. Among these, one patient discontinued the drug because of multiple AE

occurrence (skin reaction, arthralgias and myalgias, transaminases elevation, neutropenia).

Table 2 – Adverse events

Adverse events	Population (n=224)
Occurrence of one or more AE	99 (44%)
Skin reaction at injection site	86 (38%)
Arthralgias and myalgias	13 (6%)
Transaminases elevation (SGOT, SGPT)	7 (3%)
Infections	6 (3%)
Neutropenia (<1.5x10^9/L)	3 (1%)
Hypereosinophilia	1 (0.4%)
Mild serotine fever	1 (0.4%)
Hot flashes and sweating	1 (0.4%)
Perforated diverticulitis	1 (0.4%)
Optic Neuritis	1 (0.4%)
AE requiring permanent anakinra discontinuation	7 (3%)
Skin reaction	3
Infection (skin abscess)	1
Perforated diverticulitis	1
Arthralgias and myalgias	1
Multiple side effects (skin reaction, arthralgias and myalgias, transaminases elevation, neutropenia)	1

Values are presented as No. (%); AE=adverse event

Treatment duration and tapering

Patients were treated with full-dose anakinra for a median duration of 6 months (IQR 3-12), followed by a tapering period with a median duration of 3 months (IQR 0-6). Tapering modality varied across patients and centers, as described in Table 3.

Almost half patients (44%) suspended gradually the active drug, while other 17% patients abruptly interrupted the treatment.

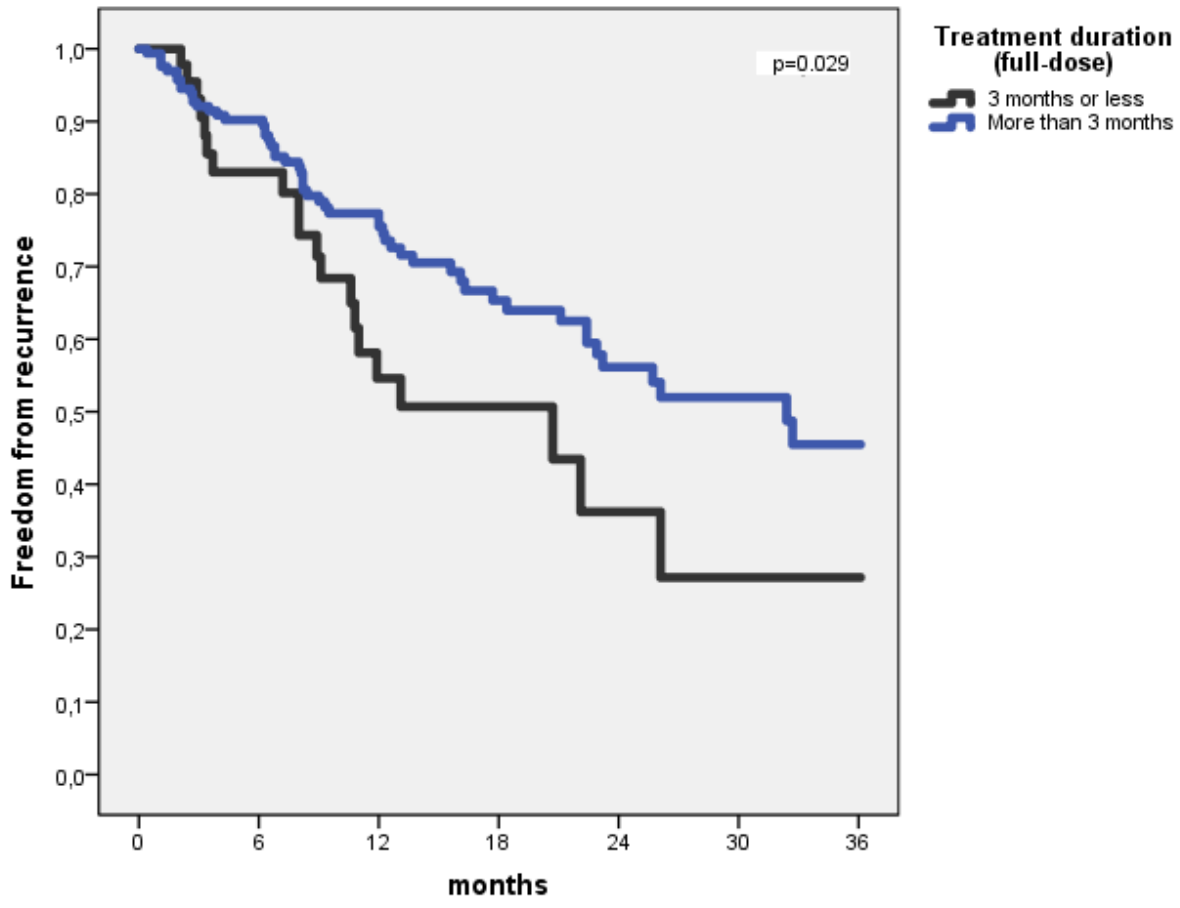
Table 3 – Tapering modality

Tapering modality	No. of patients	Pericarditis recurrence at 36 months*
Reduce to 1 dose every other day (for at least 3 months), then further reduce to half dose every other day, etc.	13	8%
Reduce to 3-4 doses per week	34	29%
Reduce to 2 doses per week	19	53%
Withdraw 1 weekly dose every 12-24 weeks	9	11%
Withdraw 1 weekly dose every 4-6 weeks	6	33%
Withdraw 1 weekly dose every 1-2 weeks	18	88%
No tapering: sudden termination	39	90%

Values are presented as No. (%)
*Risk estimated with Kaplan-Meier analysis (p<0.001).

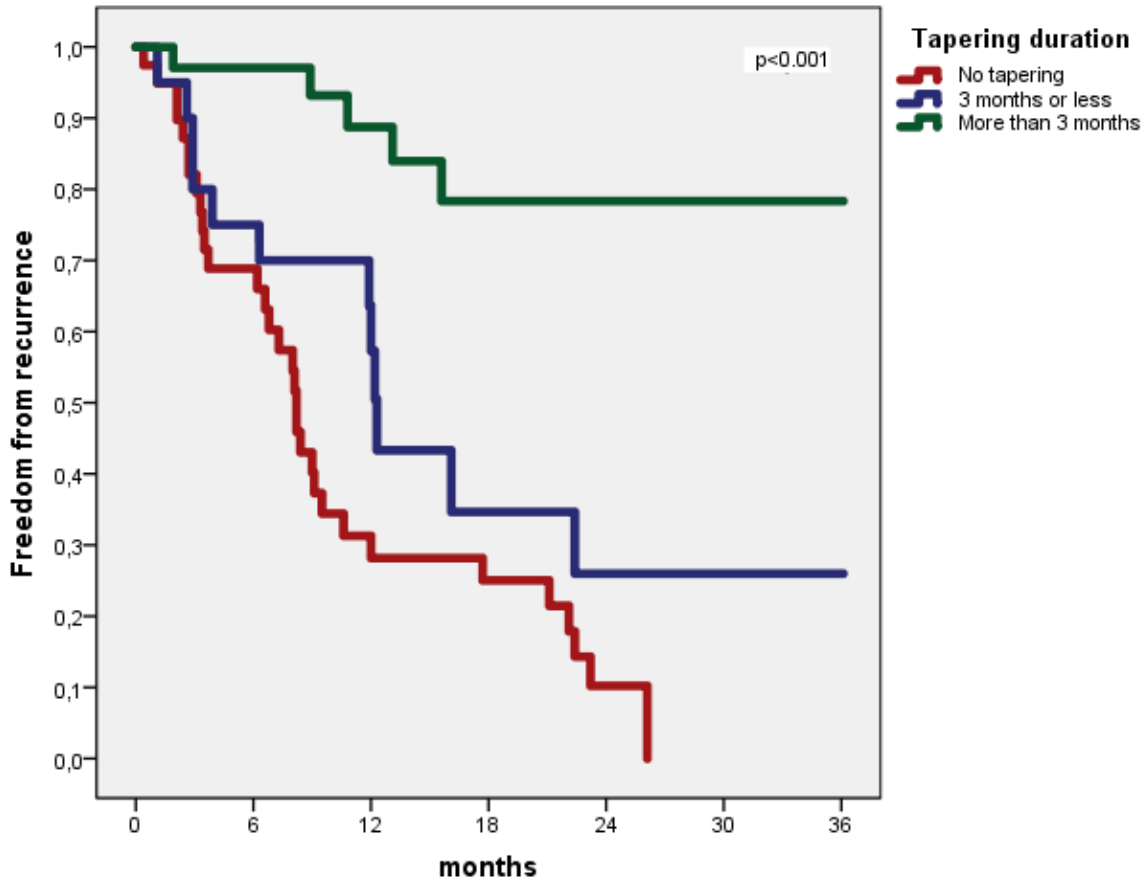
Patients who received a full-dose treatment for more than 3 months had a lower recurrence rate at 36 months (54% vs. 72%, p=0.029), as shown in Kaplan-Meier curves in Figure 2.

FIGURE 2



All patients who abruptly discontinued anakinra had one or more recurrences within 36 months. Among other patients who suspended gradually anakinra, those with a short tapering (3 months or less) had a higher 36-months recurrence rate compared with those with a long tapering (more than 3 months) (74% vs. 21%, p<0.001) as shown in Kaplan-Meier curves in Figure 3.

FIGURE 3



Baseline and drug management factors associated with pericarditis recurrence

As to further investigate the association of baseline factors and drug management factors with pericarditis recurrence, an univariate analysis was carried out and the following variables showed a significant correlation with the risk of recurrence during

follow-up: autoimmune etiology, pericardial effusion at anakinra start, discontinuation of anakinra treatment, full-dose treatment longer than 3 months, tapering duration longer than 3 months. Such factors were then evaluated with a Cox-regression analysis to appraise the independent weight of each factor on the risk of recurrence over time, as shown in Table 4.

A longer duration of full-dose treatment (p=0.009, RR=0.41) and a longer duration of tapering (p=0.009, RR=0.19) were independent predictors of 36-months freedom from any recurrence.

Table 4 – Cox regression analysis

Factors	p-value	RR	95% CI
Autoimmune etiology	0.109	2.00	0.86 – 4.71
Pericardial effusion at anakinra start	0.323	1.69	0.60 – 4.76
Permanent discontinuation of anakinra treatment (for any reason, included treatment completion)	0.134	1.64	0.86 – 3.12
Full-dose treatment longer than 3 months	**0.009**	0.41	0.21 – 0.80
Tapering duration longer than 3 months	**<0.001**	0.19	0.08 – 0.47

DISCUSSION

This is the first international registry on the use of anakinra in patients with corticosteroid-dependent and colchicine-resistant refractory recurrent pericarditis. Its clinical management is challenging since patients do not respond to colchicine and are corticosteroid-dependent, being unable to suspend them without incurring in recurrences. According to 2015 guidelines of the European Society of Cardiology[7], anakinra may be considered as a third-line option in this context. This recommendation has a low level of evidence (C, based on case series and expert opinion) in the absence of strong evidence in literature (single case reports, some case series and a recently published trial on 21 patients not available at the time of 2015 ESC guidelines publication[26]).

Two hundred twenty-four patients were included in this study, with a mean pericardial disease duration of 27 months and a mean of 5.3 previous recurrences before the starting of anakinra 100mg/day sc.

The main findings of this registry are that anakinra dramatically decreased pericarditis recurrence rate (6-fold reduction, from 2.33 flares-patient/year to 0.39 flares-patient/year), ED admissions (11-fold reduction, from 1.08 admissions-patient/year to 0.10 admissions-patient/year), hospitalizations (7-fold reduction, from 0.99 hospitalizations-patient/year to 0.13 hospitalizations-patient/year) and corticosteroids dependence (before anakinra 80% patients were on active treatment, after 27%).

Anakinra allowed a reduction in pericarditis burden from a mean of one recurrence every 157 days to a mean of one every 939 days. At 36 months after anakinra initiation, 43% patients were in stable remission without any recurrence while 29% other patients had only a single recurrence over the entire period. Compared with the only available trial[26] on 21 patients (AIRTRIP), the efficacy of anakinra is confirmed also in a real life population. Indeed, the proportion of patients with stable remission at 8 months was 82% in the AIRTRIP and 82% in this study, with only a slight difference in the incidence rate: 0.11 flares-patient/year in the AIRTRIP and 0.39 flares-patient/year in this real-world registry.

Treatment with anakinra allowed corticosteroids withdrawal in most patients, with only 27% patients still on corticosteroid treatment during the follow-up. This is important since corticosteroids side effects may be severe and affect up to 25% of chronically treated patients[4].

Chronic inflammation underlying recurrent pericarditis is probably determined by an amplified and self-sustained auto-inflammatory or auto-immune response following different exogenous or endogenous triggers[5,6]. Anakinra is a recombinant IL-1 receptor antagonist which inhibits IL-1 action, recently promising in the setting of recurrent

pericarditis but already used since more than 15 years for the treatment of rheumatoid arthritis and various monogenic and polygenic systemic autoinflammatory disease (such as TRAPS and FMF)[5]. The results of our study further confirm the critical role of IL-1 in RRP pathogenesis.

The safety profile of anakinra is reassuring in a real-world population: no life-threatening AE were recorded and most of them were mild, predominantly related to transient local skin reactions, with an incidence (38%) in line with previous studies (44%)[29]. Skin reactions can be treated with oral antihistamines and topical corticosteroids. Furthermore, their occurrence can be limited by warming anakinra syringe to room temperature before use, along with application of a cold pack to the area of injection for some minutes before and after drug administration[30]. Among other AE we observed: arthralgias and myalgias (6%), transaminases elevation (3%), neutropenia (1%). These two latter AE had been previously reported in literature with an incidence of respectively 14%[26] and 1.5%[31]. Significant infections during treatment with IL-1 antagonists are rare: in a review of clinical trials[32], they occurred in 1.7% patients, mostly respiratory and soft-tissue infections. In the present real-world registry, we observed 6 infections (3%), predominantly involving the respiratory system and soft-tissues, which were all resolved with proper treatment. Seven patients (3%) required permanent anakinra discontinuation because of AE.

A recent review by Lazaros et al.[5], investigating current evidence and future challenges on anakinra treatment for RRP, underlined that the main unresolved issues in this area were the duration of initial treatment and the tapering protocol. To address this purpose, this registry demonstrated that both a full-dose treatment duration of at least 3 months is associated with a lower risk (RR=0.41) of 36-month recurrence rate (54%) as long as a more cautious tapering of at least 3 months, which is associated with a lower risk (RR=0.19) of 36-month recurrence (21%). The tapering scheme associated with the lowest

risk of recurrence is to reduce to 1 dose every other day (for at least 3 months), then further reduce slowly to half dose every other day, etc.

The main limitation of this study is its observational design. Larger randomized and controlled trials should be done in the future to confirm these findings in comparison with a placebo-control group. However, the main strength is that provides encouraging data regarding the efficacy and safety of anakinra also in a real-world population.

In conclusion, anakinra is a safe and efficacious option for corticosteroid-dependent and colchicine-resistant refractory recurrent pericarditis despite optimal anti-inflammatory therapy (NSAIDs, colchicine and corticosteroids). A full-dose treatment duration of at least 3 months followed by a tapering period of at least 3 months were the therapeutic schemes associated with a low risk of recurrence.

REFERENCES

1. Imazio M, Belli R, Brucato A, Cemin R, Ferrua S, Beqaraj F, Demarie D, Ferro S, Forno D, Maestroni S, Cumetti D, Varbella F, Trinchero R, Spodick DH, Adler Y. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. *Lancet* 2014;**383**:2232–2237.

2. Imazio M, Brucato A, Cemin R, Ferrua S, Belli R, Maestroni S, Trinchero R, Spodick DH, Adler Y, CORP (COlchicine for Recurrent Pericarditis) Investigators. Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med* 2011;**155**:409–414.

3. Lilly LS. Treatment of acute and recurrent idiopathic pericarditis. *Circulation* 2013;**127**:1723–1726.

4. Farand P, Bonenfant F, Belley-Côté EP, Tzouannis N. Acute and recurring pericarditis: More colchicine, less corticosteroids. *World J Cardiol* 2010;**2**:403–407.

5. Lazaros G, Antonatou K, Vassilopoulos D. The Therapeutic Role of Interleukin-1 Inhibition in Idiopathic Recurrent Pericarditis: Current Evidence and Future Challenges. *Front Med (Lausanne)* 2017;**4**:78.

6. Pathak S, McDermott MF, Savic S. Autoinflammatory diseases: update on classification diagnosis and management. *J Clin Pathol* 2017;**70**:1–8.

7. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lionis C, Maisch B, Mayosi B, Pavie A, Ristic AD, Sabaté Tenas M, Seferovic P, Swedberg K, Tomkowski W, ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery

(EACTS). *Eur Heart J* 2015;**36**:2921–2964.

8. Vassilopoulos D, Lazaros G, Tsioufis C, Vasileiou P, Stefanadis C, Pectasides D. Successful treatment of adult patients with idiopathic recurrent pericarditis with an interleukin-1 receptor antagonist (anakinra). *Int J Cardiol* 2012;**160**:66–68.

9. Scardapane A, Brucato A, Chiarelli F, Breda L. Efficacy of an interleukin-1β receptor antagonist (anakinra) in idiopathic recurrent pericarditis. *Pediatr Cardiol* 2013;**34**:1989–1991.

10. Camacho-Lovillo M, Méndez-Santos A. Successful treatment of idiopathic recurrent pericarditis with interleukin-1 receptor antagonist (Anakinra). *Pediatr Cardiol* 2013;**34**:1293–1294.

11. Picco P, Brisca G, Traverso F, Loy A, Gattorno M, Martini A. Successful treatment of idiopathic recurrent pericarditis in children with interleukin-1beta receptor antagonist (anakinra): an unrecognized autoinflammatory disease? *Arthritis Rheum* 2009;**60**:264–268.

12. Picco P, Naselli A, Pala G, Marsciani A, Buoncompagni A, Martini A. Recurrent pericarditis in Myhre syndrome. *Am J Med Genet A* 2013;**161A**:1164–1166.

13. Massardier C, Dauphin C, Eschalier R, Lusson JR, Soubrier M. Resistant or recurrent acute pericarditis: a new therapeutic opportunity? *Int J Cardiol* 2014;**177**:e75-77.

14. Emmi G, Barnini T, Silvestri E, Milco D'Elios M, Emmi L, Prisco D. A new case of idiopathic recurrent acute pericarditis due to R104Q mutation in TNFRSF1A successfully treated with anakinra: expanding the questions. *Clin Exp Rheumatol* 2014;**32**:297.

15. Tomelleri A, Cavalli G, De Luca G, Campochiaro C, D'Aliberti T, Tresoldi M, Dagna L. Treating Heart Inflammation With Interleukin-1 Blockade in a Case of Erdheim-Chester Disease. *Front Immunol* 2018;**9**:1233.

16. Cantarini L, Lucherini OM, Cimaz R, Galeazzi M. Recurrent pericarditis caused by a

rare mutation in the TNFRSF1A gene and with excellent response to anakinra treatment. *Clin Exp Rheumatol* 2010;**28**:802.

17. Camprubí D, Mitjavila F, Arostegui JI, Corbella X. Efficacy of anakinra in an adult patient with recurrent pericarditis and cardiac tamponade as initial manifestations of tumor necrosis factor receptor-associated periodic syndrome due to the R92Q TNFRSF1A variant. *Int J Rheum Dis* 2017;**20**:510–514.

18. Insalaco A, Prencipe G, Buonuomo PS, Ceccherini I, Bracaglia C, Pardeo M, Nicolai R, De Benedetti F. A novel mutation in the CIAS1/NLRP3 gene associated with an unexpected phenotype of cryopyrin-associated periodic syndromes. *Clin Exp Rheumatol* 2014;**32**:123–125.

19. Ozturk K, Deveci M, Ekinci Z. Refractory idiopathic recurrent pericarditis: treatment with interleukin-1 receptor antagonist is an option! *J Cardiovasc Med (Hagerstown)* 2017;**18**:731.

20. Baszis KW, Singh G, White A, Thatayatikom A. Recurrent cardiac tamponade in a child with newly diagnosed systemic-onset juvenile idiopathic arthritis. *J Clin Rheumatol* 2012;**18**:304–306.

21. Scott IC, Hajela V, Hawkins PN, Lachmann HJ. A case series and systematic literature review of anakinra and immunosuppression in idiopathic recurrent pericarditis. *Journal of Cardiology Cases* 2011;**4**:e93–e97.

22. Finetti M, Insalaco A, Cantarini L, Meini A, Breda L, Alessio M, D'Alessandro M, Picco P, Martini A, Gattorno M. Long-term efficacy of interleukin-1 receptor antagonist (anakinra) in corticosteroid-dependent and colchicine-resistant recurrent pericarditis. *J Pediatr* 2014;**164**:1425-1431.e1.

23. Lazaros G, Vasileiou P, Koutsianas C, Antonatou K, Stefanadis C, Pectasides D, Vassilopoulos D. Anakinra for the management of resistant idiopathic recurrent

pericarditis. Initial experience in 10 adult cases. *Ann Rheum Dis* 2014;**73**:2215–2217.

24. Jain S, Thongprayoon C, Espinosa RE, Hayes SN, Klarich KW, Cooper LT, Moder KG, Anavekar NS, Oh JK, Matteson EL. Effectiveness and Safety of Anakinra for Management of Refractory Pericarditis. *Am J Cardiol* 2015;**116**:1277–1279.

25. Imazio M, Brucato A, Pluymaekers N, Breda L, Calabri G, Cantarini L, Cimaz R, Colimodio F, Corona F, Cumetti D, Cuccio CDBL, Gattorno M, Insalaco A, Limongelli G, Russo MG, Valenti A, Finkelstein Y, Martini A. Recurrent pericarditis in children and adolescents: a multicentre cohort study. *J Cardiovasc Med (Hagerstown)* 2016;**17**:707–712.

26. Brucato A, Imazio M, Gattorno M, Lazaros G, Maestroni S, Carraro M, Finetti M, Cumetti D, Carobbio A, Ruperto N, Marcolongo R, Lorini M, Rimini A, Valenti A, Erre GL, Sormani MP, Belli R, Gaita F, Martini A. Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence: The AIRTRIP Randomized Clinical Trial. *JAMA* 2016;**316**:1906–1912.

27. Imazio M, Brucato A, Cemin R, Ferrua S, Maggiolini S, Beqaraj F, Demarie D, Forno D, Ferro S, Maestroni S, Belli R, Trinchero R, Spodick DH, Adler Y, ICAP Investigators. A randomized trial of colchicine for acute pericarditis. *N Engl J Med* 2013;**369**:1522–1528.

28. Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet* 2007;**370**:1453–1457.

29. Lazaros G, Imazio M, Brucato A, Vassilopoulos D, Vasileiou P, Gattorno M, Tousoulis D, Martini A. Anakinra: an emerging option for refractory idiopathic recurrent pericarditis: a systematic review of published evidence. *J Cardiovasc Med (Hagerstown)*

2016;**17**:256–262.

30. Kaiser C, Knight A, Nordström D, Pettersson T, Fransson J, Florin-Robertsson E, Pilström B. Injection-site reactions upon Kineret (anakinra) administration: experiences and explanations. *Rheumatol Int* 2012;**32**:295–299.

31. Campion GV, Lebsack ME, Lookabaugh J, Gordon G, Catalano M. Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. The IL-1Ra Arthritis Study Group. *Arthritis Rheum* 1996;**39**:1092–1101.

32. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis* 2009;**68**:25–32.